

## PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING  
AMENDMENTS OF THE CLAIMS(PCT Rule 62 and  
Administrative Instructions, Section 417)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as International Preliminary Examining Authority

Date of mailing:

06 October 1997 (06.10.97)

International application No.:

PCT/US97/02094

International filing date:

07 February 1997 (07.02.97)

Applicant:

RUTGERS, THE STATE UNIVERSITY et al

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417)

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

Beatriz Morariu

Telephone No.: (41-22) 338.83.38

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>42931-49411-MC</b>	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/SE 97/02094</b>	International filing date (day/month/year) <b>12 December 1997</b>	(Earliest) Priority Date (day/month/year) <b>12 December 1996</b>
Applicant <b>Karolinska Innovation AB et al</b>		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (See Box I).
2. ☐ Unity of invention is lacking (See Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ transcribed by this Authority.
4. With regard to the title, ☐ the text is approved as submitted by the applicant.  
☒ the text has been established by this Authority to read as follows:  
 Therapeutic applications of antigens or epitopes associated with impaired cellular peptide processing, e.g. expressed on RMA-S cells transfected with a B7-1 gene
5. With regard to the abstract, ☒ the text is approved as submitted by the applicant.  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:  
 Figure No.     --     ☐ as suggested by the applicant. ☐ None of the figures.  
☐ because the applicant failed to suggest a figure.  
☐ because this figure better characterizes the invention.

**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claim 12 relate to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1.(iv).  
Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

- The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/02094

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 39/00, A61K 45/05, A61K 48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
TS 1 70/25 X	Journal of immunology, Volume 156, 1996, S. K. Nair et al, "Cells Treated with TAP-2 Antisense Oligonucleotides Are Potent Antigen-Presenting Cells In Vitro and In Vivo", page 1772 - page 1780, see page 1778 - page 1779 and figures 6 and 7 --	1-12
ITS 2 970625 X	Dialog Information Services, File 159, Cancerlit, Dialog accession no. 01240395, Cancerlit accession no. 96614957, Mayordomo JI et al: "Proc Annu Meet Am Soc Clin Oncol; 14:A1809 1995 --	1-12

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

23 March 1998

Date of mailing of the international search report

26 -03- 1998

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Carl-Olof Gustafsson  
Telephone No. +46 8 782 25 00

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
3. X	Eur. J. Immunol., Volume 23, 1993, L. Franksson et al, "Immunization against tumor and minor histocompatibility antigens by eluted cellular peptides loaded on antigen processing defective cells", page 2606 - page 2613, see table 2 and page 2611 - page 2612 --	1,2,6-9
4. A	EP 0600591 A2 (BRISTOL-MYERS SQUIBB COMPANY), 8 June 1994 (08.06.94), see claims and page 4 - page 6 --	1-11
5. A	Journal of immunology, Volume 154, No 7, 1995, Tianmin Liu et al, "Heat-Inactivated Sendai Virus Can Enter Multiple MHC Class I Processing Pathways and Generate Cytotoxic T Lymphocyte Responses In Vivo" page 3147 - page 3155	1-8,10,11
X	--	9
6. A	Scand. J. Immunol., Volume 42, 1995, X. Zhou et al, "Characterization of TAP-Independent and Brefeldin A-Resistant Presentation of Sendai Virus Antigen to CD8+ Cytotoxic T Lymphocytes" page 66 - page 75	1-8,10,11
X	--	9
7. X	CH 647152 A5 (PROF. DR. HANS LIMBURG), 15 January 1985 (15.01.85) --	9
8. X	DE 2024458 A (HARTMANN GEB. UNGEWITTER), 2 December 1971 (02.12.71) --	9

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/02094

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
9. A	Proc. Natl. Acad. Sci., Volume 90, November 1993, R. A. Hendersson et al, "Direct identification of an endogenous peptide recognized by multiple HLA-A2.1-specific cytotoxic T cells", page 10275 - page 10297, see page 10277 - page 10279 --	1-11
10. A	WO 9324525 A1 (RIJKSUNIVERSITEIT LEIDEN), 9 December 1993 (09.12.93), see page 2, line 26 - page 3; page 7, line 15 - line 24 --	1,4,6-9
11. A	WO 9609380 A1 (THE UNIVERSITY OF BRITISH COLUMBIA), 28 March 1996 (28.03.96) --	1
12. P,A	WO 9707128 A1 (DUKE UNIVERSITY), 27 February 1997 (27.02.97), see page 3 - page 5; page 9 - page 14, examples and claims	
P,X	----- --	9,10,11

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

02/03/98

International application No.

PCT/SE 97/02094

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0600591 A2	08/06/94	AU 662450 B AU 4877293 A CA 2107537 A JP 7069928 A MX 9306147 A	31/08/95 14/04/94 03/04/94 14/03/95 30/06/94
CH 647152 A5	15/01/85	AT 369653 B AU 5806980 A CA 1139219 A DD 150545 A DE 2918927 A DK 189580 A EP 0019167 A,B FI 801420 A FR 2455891 A,B GB 2048069 A,B JP 55151515 A ZA 8002391 A	25/01/83 13/11/80 11/01/83 09/09/81 20/11/80 11/11/80 26/11/80 11/11/80 05/12/80 10/12/80 26/11/80 29/04/81
DE 2024458 A	02/12/71	NONE	
WO 9324525 A1	09/12/93	AU 681853 B AU 4359193 A CA 2136624 A EP 0643726 A JP 8501280 T US 5679641 A	11/09/97 30/12/93 09/12/93 22/03/95 13/02/96 21/10/97
WO 9609380 A1	28/03/96	EP 0783573 A	16/07/97
WO 9707128 A1	27/02/97	AU 7008896 A	12/03/97

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 42931-49411-MC	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE97/02094	International filing date ( <i>day/month/year</i> ) 12.12.1997	Priority date ( <i>day/month/year</i> ) 12.12.1996
International Patent Classification (IPC) or national classification and IPC <sub>6</sub> A 61 K 39/00, A 61 K 45/05, A 61 K 48/00		
Applicant Karolinska Innovation AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of \_\_\_\_\_ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  03.07.1998	Date of completion of this report  06.04.1999
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer  Carl-Olof Gustafsson Telephone No. 08-782 25 00



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE97/02094

## I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

- ☒ the international application as originally filed.
- ☐ the description, pages \_\_\_\_\_, as originally filed,  
 pages \_\_\_\_\_, filed with the demand,  
 pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
 pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☐ the claims, Nos. \_\_\_\_\_, as originally filed,  
 Nos. \_\_\_\_\_, as amended under Article 19,  
 Nos. \_\_\_\_\_, filed with the demand,  
 Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
 Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
 sheets/fig \_\_\_\_\_, filed with the demand  
 sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
 sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, Nos. \_\_\_\_\_
- ☐ the drawings, sheets/fig \_\_\_\_\_

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12

because:

☒ the said international application, or the said claims Nos. 12

relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. \_\_\_\_\_

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Claims	<u>3, 5</u>	YES
	Claims	<u>1, 2, 4, 6-11</u>	NO
Inventive step (IS)	Claims	<u>3, 5</u>	YES
	Claims	<u>1, 2, 4, 6-11</u>	NO
Industrial applicability (IA)	Claims	<u>1-11</u>	YES
	Claims		NO

**2. Citations and explanations**

The present invention pertains to the use of a substance that impairs cellular peptide processing for MHC presentation for the preparation of a pharmaceutical agent or vaccine that can stop or prevent cancer growth or virus infection by stimulating immunological effectors (CD8 cells or cytotoxic cells) associated with (MHC class I dependent) impaired cellular peptide processing. Preferred substances are those that inhibit transporters associated with antigen processing (TAP), e.g. ICP47 or a gene encoding a TAP inhibitor or antisense oligonucleotides. Further preferred substances are those inhibiting the function of and /or the expression of proteasome.

A further use for preparing a pharmaceutical composition is given in claim 4 and involves antigens or epitopes associated with impaired cellular peptide processing (peptides or parts of MHC class I molecules). Such use elicits specific T-cells against antigens/epitopes associated with impaired cellular peptide processing. The wording of claim 4 is, however, not clear and concise as it is not clearly stated that the active component of the pharmaceutical composition "consists of antigens and epitopes associated with..." and not specific T-cells directed against these antigens/epitopes (inserting "able to elicit..." would probably solve this problem).

According to claim 5, molecules directed against MHC class I dependent antigens/epitopes associated with impaired cellular peptide processing (e.g. receptors) can also be used in pharmaceutical compositions. However, the definition of the molecules is vague (except for T-cell receptors) and it is not obvious from the description what advantages the treatment with such compounds achieves.

.../...

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Claims 6 and 7 refer to cells that express antigens associated with impaired cellular peptide processing to be used for preparing a pharmaceutical or vaccine against cancer or virus infection.

Claim 8 refers to lymphoid cells *activated against* antigens or epitopes associated with impaired cellular peptide processing, e.g. lacking TAP function. Claims 6-8 are formulated as first medical indication claims.

Claim 9 refers to a process for *induction of* antigens/epitopes associated with impaired cellular peptide processing by treating cells with, e.g., TAP or proteasome inhibiting agents or antisense nucleotides or ribozyme or a DNA sequence coding for such inhibiting agents. Steps e and f make use of "and" and "or" in a way that makes the claim difficult to interpret. The claim seems to refer to the induction of such antigens/epitopes by means of transfection of, e.g., insect cells with MHC-class I molecules and to irradiation of cells; at least, the treatment of cells with radiation is well known to a person skilled in the art.

Claim 10 refers to a "kit" consisting of one component: a substance that induces antigens or epitopes associated with impaired cellular peptide processing (on exposed cells/in the exposed human or animal body?). The claim lacks the necessary second or more components in order to define a "kit". Furthermore, the claim does not reveal any use (e.g. "in vitro stimulation of cells" or similar). In the absence of second or more obligatory components and in the absence of a use, the claim may define a "first medical indication" type claim and is handled accordingly.

Claim 11 refers to a composition or a vaccine comprising a pharmaceutical effective dose of the components mentioned in claims 1-4.

The International Search Report revealed several documents considered to be of particular relevance. Nair SK et al., J. Immunology vol. 156, 1996, p. 1772 ff, in particular pp. 1778-9 and figs. 6 and 7, refer to treatment of antigen presenting cells with TAP2 antisense oligonucleotides. Use of antisense oligonucleotides in adoptive immunotherapy is emphasised and the use of TAP-2 inhibited cells as potent inducers of immunity in vivo in active immunotherapy (p1779 second paragraph) is suggested. Consequently, the use according to claims 1, 2 and 4 and the use of cells and the kit or process according to claims 6-11 are considered to lack novelty.

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Mayordomo JI et al., Cancerlit ref. 96614957, Dialog Acc. no 1240395, abstract of Proc. Annu. Meet. Am. Soc. Clin. Oncol.;14:A1809, 1995, refer to use of peptide pulsed dendritic cells and TAP-deficient cells as effective immunogens in tumour vaccines. Accordingly, the cells to be used for preparing a vaccine according to claims 6 and 7 lack novelty.

Franksson L et al., Eur. J. Immunol. vol 23, 1993, pp 2606-13 see in particular table 2 and pages 2611-12, reveal the use of peptides loaded on antigen processing defective cells for the activation of tumour antigen specific CTL. Bridging parts of pages 2611-12 states that "peptide loaded TAP2-deficient cells allowed immunisation with limited amounts of naturally processed peptides". The deficient cells acted as an antigen carrier for e.g. tumour specific antigens (table 2). Virus antigens are also suggested. The use according to claims 1, 2 and 4 and the use of cells, the kit or process according to claims 6-11 are considered to lack novelty in view of Franksson et al..

Liu T et al., J. Immunol. vol. 154, 1995, pp 3147-54 and Zhou X et al., Scand. J immunol. vol 42, 1995, pp 66-75 and patents CH647152 and DE2024458 cited in the Report as particularly relevant to claim 9, reveal methods for treating cells in order to induce an antigen response. Liu et al. cells (p 3148 and fig 2) and Zhou et al (see "Discussion") teach CTL recognition of TAP independent, antigen processing. The patent documents reveal radiation or cytostatic treated tumour cells for immunisation purposes. The method according to claim 9 is considered to lack novelty in view of these documents.

4 A novel solution to the problem of inducing immunity to virus infection or cancer, offered by the present invention, is considered to be the use of certain inhibitors (e.g. ICP47), not formerly being applied in such treatment! However, none of the claims have been restricted to such use although claim 9 a) refers to a process for induction of antigens or epitopes with the aid of e.g. ICP47 "together with a pharmaceutically acceptable adjuvant" as one alternative.,